REMARKS

Claims 58, 68, 73 and 80-81 are pending in the application. Claims 60, 66 and 74-76 are newly cancelled. Claims 58, 68 and 73 are newly amended. Claims 80-81 are newly added. Support for claims amendments is found throughout the specification and in the originally filed claims and is discussed below. No new matter is added.

Compact Disc Submission

The Office Action states that the specification is objected to because the incorporation by reference of the compact disc added in the amendment filed 12/16/05 is not proper, and states that copy 1 and copy 2 of the discs were not the same.

Applicant notes that according to Appendix R PATENT RULES, § 1.52 (e)(4) provides that "In the event that the two compact discs are not identical, the Office will use the compact disc labeled "Copy 1" for further processing".

However, in order to expedite prosecution, this reply includes a compact disc in duplicate containing a sequence listing (2 compact discs: Revised Sequence Listing - Copy 1 and Revised Sequence Listing - Copy 2), which are hereby incorporated by reference in their entirety. Each compact disc is identical and contains the following sequence listing file:

DESCRIPTION	SIZE	CREATED	Text File Name
1 Revised Sequence Listing	36.3 MB	01/02/2007	Revised Sequence Listing Dec29 2006.TXT

35 U.S.C. § 112, 1st Paragraph Rejections - Enablement

Claims 58, 60, 66, 68 and 73-76 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. Applicant respectfully traverses the rejections.

The Office action notes that the strongest relative differences with respect to relative frequency analysis between the disclosed libraries were observed for CALM1, but asserts there are many unresolved issues before reliable conclusions can be drawn in the diagnosis or staging of OA using just this gene or a group of genes comprising this gene as an indicator.

One of these unresolved issues asserted in the Office Action includes the lack of statistics disclosed in the specification. The Office Action further states that the declaration provides statistical analysis of only the difference between OA and normal test samples, whereas many of the instant claims set forth conclusions that "mild" or "severe" OA are present.

Accordingly, in the interest of expediting prosecution of the application, but without prejudice to Applicant's rights to later pursue related claims, Applicant has canceled claims 60, 66 and 75-76, drawn to mild or severe OA, thereby addressing this issue of statistics.

Another of these unresolved issues asserted in the Office Action concerns ambiguity regarding what level of difference in expression is diagnostic of OA or a stage of OA, asserting that the claims set forth that any difference in expression levels is sufficient to draw conclusions regarding the indication of OA, or regarding the presence of OA.

Accordingly, in the interest of expediting prosecution of the application, but without prejudice to Applicant's rights to later pursue related claims, Applicant has canceled claims 74-76 drawn to conclusions regarding the presence of OA, and has amended independent claim 58, drawn to the indication of OA, such that conclusions regarding the indication of OA are drawn as a result of determination of significantly higher expression of tumor necrosis factor alpha-induced protein 6 and CALM1, and significantly lower expression of LAMC1, in cartilage from said individual suspected of having or being afflicted with osteoarthritis than in cartilage from individuals not having osteoarthritis. Support for reciting "significantly" altered gene expression between cartilage from normal and osteoarthritic individuals can be found in the specification, for example, at paragraph 391 of the published application (US20040037841).

Applicant has also added new claims 80 and 81, which are dependent from newly amended claim 58, and which contain the limitation that the ratio of the level of CALM1 transcripts in normal to osteoarthritic cartilage is at least 0.25% to 0.13%, or at least 0.32% to

0.13%. Specification support for these ratios is clearly provided at Table 6, entry #29. One of ordinary skill in the art will readily understand from the specification that the fact that CALM1 transcript levels increase as a function of OA severity (normal: 0.13%; mild OA: 0.25%; and severe OA: 0.32%) clearly teaches that significantly increased CALM1 cartilage transcript levels relative to normal cartilage will be indicative of OA. The artisan will further readily grasp from the specification teachings that a ratio of CALM1 transcript levels in cartilage of a test individual to those in normal individuals of at least 0.25%:0.13% will be indicative of OA in the test individual, and that such a ratio of at least 0.32%:0.13% will be further indicative of OA in the test individual. The concept of ratios of differential expression levels is adequately discussed in the specification, for example at paragraph 126 of the published application. As such, it is Applicant's position that the specification clearly teaches the ordinarily skilled artisan how to determine indication of OA according to the instantly claimed method, and that the Examiner's remarks regarding what difference in gene expression of the three elected genes is diagnostic of OA are adequately addressed.

The final of these unresolved issues asserted in the Office Action is whether the test of relative EST frequency is valid given that the total pool of ESTs tested in each sample is different, if a change in relative frequency is a result of differences in expression levels of other genes that cause the total number of expressed genes to increase or decrease relative to the gene in question. The Office Action asserts that Kumar et al. "caution against being overreaching regarding conclusions" and in reference to quotes from Kumar et al. regarding the functionality of transcripts which are observed to be differentially expressed at low levels via EST frequency analysis. These assertions are based on the following Kumar et al. citations: "*It is not clear if such low level of expression is functionally relevant*" (p. 650, 1st column); and "*To begin to understand function, the expression pattern of these genes first needs to be compared using additional approaches such as Northern blotting and in situ hybridization. If confirmed, further evaluation of patterns by quantitative and biochemical analyses would be required*" (bridging p. 650-651).

Applicant respectfully submits, however, that disease-specific differential gene expression can simply be a downstream effect of pathogenic processes which lacks any relevant function associated with disease which can be understood in the sense of the cited passages of

Kumar et al. which appear to address an issue of purely scientific interest. Even assuming that a given empirically determined disease-specific differential gene expression pattern, such as that upon which the claims are based, have a putative disease-related "function", **an understanding of such function is clearly not necessary to enable exploitation of knowledge of such patterns towards disease diagnosis**. For example prostate-specific phosphatase and prostate-specific antigen (PSA) were long used as disease markers without an understanding of their function (refer, for example, to the enclosed abstracts of Chu TM, 1990, (Prostate cancer-associated markers. Immunol. Ser. 53:339-56) and of Diamandis, 2000(Prostate-specific antigen: a cancer fighter and a valuable messenger? Clin Chem. 46:896-900), respectively. As such, Applicant submits that the rationale of the cited passages of Kumar *et al.* fails to cast doubt upon the reliability of the EST frequency analysis results disclosed in the specification for pointing to the OA-specific differential gene expression patterns upon which the claims are based.

Applicant wishes to highlight that the Examiner has indicated that the microarray data presented in the declaration filed 7/17/06 clearly supports the assertion that the three genes whose transcripts are required by the claims are differentially regulated in patients with OA versus those without OA, namely that there is up regulation in the case of TNFAIP6 and CALM1 and down regulation in LAMC1, in accordance with the differential expression of these genes shown by the EST frequency analysis data disclosed in the specification. It is worth noting, in view of the Kumar *et al.* teaching cited by the Examiner whereby complementary analytical methods may be used to validate EST frequency analysis, that the statistically significant confirmatory data of the declaration were obtained using the alternate method of microarray hybridization analysis, using different subjects than those which were used to generate the EST frequency data disclosed in the specification with respect to these genes.

In view of Applicant's comments above regarding the EST frequency data disclosed in the specification, and in view of the supporting microarray data presented in the declaration, Applicants submit that the test of relative EST frequency is valid and supports the claimed differential gene expression of the elected three genes as being indicative of OA.

The Office Action states that the scope of the claims is quite broad with regard to the comparisons in the claims encompassing the detection of only one individual versus another

individual. Solely in the interest of expediting prosecution of the application, but without prejudice to Applicant's rights to later pursue related claims, Applicant further elects to amend independent claim 58 so as to change the recitation "*one or more individuals not having OA*" to the recitation "*individuals not having osteoarthritis*", so as to no longer encompass comparison to a single individual not having OA.

In view of Applicant's arguments and amendments, reconsideration and withdrawal of the rejection is respectfully requested.

Conclusion

Applicant submits that all claims are allowable as written and respectfully requests early favorable action by the Examiner. If the Examiner believes that a telephone conversation with Applicant's attorney's/agent would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney/agent of record.

Respectfully submitted,

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Encl.

Abstract of Chu TM, 1990. Prostate cancer-associated markers. Immunol Ser. 53:339-56; and

Abstract of Diamandis EP, 2000. Prostate-specific antigen: a cancer fighter and a valuable messenger? Clin Chem. 46:896-900.

Chu TM., 1990. Immunol Ser. 53:339-56. Prostate cancer-associated markers.

Immunodiagnosis of prostate cancer is at a more advanced stage than that of most other tumors. Two well-known markers, prostatic acid phosphatase and prostate-specific antigen, have been used in the clinical management of patients. Prostate-specific antigen is a more sensitive and reliable marker than prostatic acid phosphatase. Serum prostate-specific antigen is effective in monitoring disease status, predicting recurrence, and detecting residual disease. Prostate-specific antigen is a tool for the histological differential diagnosis of metastatic carcinomas, especially in the identification of metastatic prostate tumor cells in distant organs and in the differentiation of primary prostate carcinoma from poorly differentiated transitional cell carcinoma of the bladder. Few data on biological function are available. Prostatic acid phosphatase functions as a phosphotyrosyl-protein phosphatase and prostate-specific antigen as a protease. Physiological function in the prostate remains to be elucidated. Several of the prostate-specific and prostate-tumor-associated antigens, as well as a putative prostate tumor-specific antigen, as recognized by monoclonal antibodies are available. Clinical evaluation of these potential markers is not yet available.

PMID: 1713065 [PubMed - indexed for MEDLINE]

Diamandis EP., 2000. Clin Chem. 46:896-900. Prostate-specific antigen: a cancer fighter and a valuable messenger?

BACKGROUND: Prostate-specific antigen (PSA) is a valuable prostatic cancer biomarker that is now widely used for population screening, diagnosis, and monitoring of patients with prostate cancer. Despite the voluminous literature on this biomarker, relatively few reports have addressed the issue of its physiological function and its connection to the pathogenesis and progression of prostate and other cancers. APPROACH: I here review literature dealing with PSA physiology and pathobiology and discuss reports that either suggest that PSA is a beneficial molecule with tumor suppressor activity or that PSA has deleterious effects in prostate, breast, and possibly other cancers. CONTENT: The present scientific literature on PSA physiology and pathobiology is confusing. A group of reports have suggested that PSA may act as a tumor suppressor, a negative regulator of cell growth, and an apoptotic molecule, whereas others suggest that PSA may, through its chymotrypsin-like activity, promote tumor progression and metastasis. SUMMARY: The physiological function of PSA is still not well understood. Because PSA is just one member of the human kallikrein gene family, it is possible that its biological functions are related to the activity of other related kallikreins. Only when the physiological functions of PSA and other kallikreins are elucidated will we be able to explain the currently apparently conflicting experimental data.

PMID: 10894830 [PubMed - indexed for MEDLINE]